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Circulating Angiopoietin-2 Concentrations in Neonates and Children With Sepsis Compared With Non-Septic Controls: A Systematic Review and Meta-Analysis

Saweera Khan[1]

saweerakhanresearch@gmail.com

Jinnah Sindh Medical University

Iqra Paracha[1]

Jinnah Sindh Medical University

Osama Mohsin

Jinnah Medical and Dental College

Iqra Tanzeel[1]

Jinnah Sindh Medical University

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Abstract

Purpose:

Angiopoietin-2 (Ang-2) is implicated in endothelial dysfunction during sepsis, but its association with neonatal and pediatric sepsis remains insufficiently characterized. This systematic review and meta-analysis compared circulating Ang-2 concentrations in patients with sepsis and non-septic controls.

Methods:

PubMed/MEDLINE, Embase, Scopus, the Cochrane Central Register of Controlled Trials, and Google Scholar were searched through September 5, 2026. Eleven studies were included in the systematic review. Random-effects meta-analysis pooled standardized mean differences (SMDs). Risk of bias was assessed using the Newcastle–Ottawa Scale, and certainty of evidence using GRADE.

Results:

Five studies involving 545 participants (460 with sepsis and 85 controls) contributed to the primary meta-analysis. Ang-2 concentrations were higher in patients with sepsis (SMD, 1.54; 95% CI, 0.91–2.18; $p < 0.00001$), with substantial heterogeneity ($I^2 = 75\%$). Excluding one study yielded a similar estimate (four studies; SMD, 1.41; 95% CI, 0.74–2.09; $I^2 = 78\%$). An expanded seven-study sensitivity analysis incorporating graph-derived estimates produced an SMD of 3.86 (95% CI, 2.01–5.70; $I^2 = 97\%$). Certainty of evidence was very low.

Conclusion:

Circulating Ang-2 concentrations were elevated in pediatric sepsis compared with non-septic controls. However, substantial heterogeneity and very low-certainty evidence limit clinical interpretation. Further prospective studies are needed to establish its diagnostic and prognostic utility.

What is Known

- Angiopoietin-2 is involved in endothelial dysfunction and vascular instability during sepsis.

What is New:

- This meta-analysis found higher circulating Ang-2 concentrations in pediatric sepsis than in non-septic controls.
- Substantial heterogeneity and very low-certainty evidence limit conclusions about its clinical utility.

1. Introduction

Sepsis remains a major global cause of morbidity and mortality in neonates and children. The Global Burden of Disease Study estimated 48.9 million incident cases and 11.0 million sepsis-related deaths

worldwide in 2017; children younger than five years accounted for approximately 20.3 million cases (1). Diagnosis is challenging because manifestations vary with age and severity and overlap with other acute conditions (2, 3). C-reactive protein and procalcitonin can support assessment but cannot independently establish the diagnosis (4). Biomarkers reflecting specific pathophysiological processes may therefore provide complementary information.

Endothelial dysfunction contributes to vascular permeability, microcirculatory abnormalities, and organ injury in sepsis (5, 6). Angiopoietin–Tie2 signalling regulates endothelial stability: angiopoietin-1 (Ang-1) generally supports barrier integrity, whereas angiopoietin-2 (Ang-2), released by activated endothelial cells, can oppose Ang-1-mediated signalling and promote endothelial destabilization during inflammation (5, 6). This provides a biological rationale for studying circulating Ang-2, although a plausible mechanism does not itself establish diagnostic accuracy or clinical utility. Reviews of endothelial-activation biomarkers have highlighted the challenges of translating biomarker associations into validated clinical applications (7).

Studies have examined Ang-2 in different pediatric sepsis contexts. Giuliano et al. investigated admission angiopoietin concentrations and temporal changes in children with septic shock and different levels of sepsis severity (8, 9). Wang et al. assessed Ang-1, Ang-2, and bicarbonate as potential markers in children with severe sepsis (10). In newborns, Zonneveld et al. reported higher serum Ang-2 and Ang-2/Ang-1 ratios in early-onset sepsis (11). Mankhambo et al. found higher Ang-2 among nonsurvivors with severe bacterial infection, although Ang-2 was not independently associated with mortality after adjustment (12). These studies address related but distinct outcomes; findings about severity, biomarker kinetics, or mortality do not directly quantify differences in Ang-2 between septic and non-septic children.

Quantitative synthesis is complicated by differences in age, sepsis definitions, comparator groups, specimen types, assays, and sampling times. Studies reporting adjusted associations, diagnostic performance, serial trajectories, or graphical findings without reliable numerical summaries may not be suitable for direct pooling. Synthesis methods should reflect the completeness and comparability of the available data (13, 14).

This systematic review and meta-analysis therefore evaluated circulating serum and plasma Ang-2 concentrations in neonates and children with sepsis compared with non-septic controls. The primary objective was to estimate the standardized mean difference (SMD). Secondary objectives were to assess robustness through sensitivity analyses, evaluate methodological quality and certainty of evidence, and narratively synthesize relevant studies unsuitable for quantitative pooling.

2. Materials and Methods

2.1. Study design and registration

This systematic review and meta-analysis evaluated circulating angiopoietin-2 (Ang-2) concentrations in neonates and children with sepsis compared with non-septic controls. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (15). The protocol was registered in PROSPERO (CRD420261519673; created 27 September 2026 and last edited 28 September 2026).

2.2. Eligibility criteria

Studies were eligible if they included neonates, infants, children, or adolescents younger than 18 years; evaluated participants with suspected or confirmed sepsis, severe sepsis, or septic shock; measured Ang-2 in serum or plasma; and included a non-septic comparison group. Eligible designs included observational and comparative clinical studies reporting quantitative Ang-2 data or relevant findings concerning sepsis severity, organ dysfunction, mortality, or diagnostic performance.

Studies were excluded if they were reviews, protocols, editorials, case reports, or animal studies; lacked an eligible non-septic comparator; or did not provide sufficient information for a relevant comparison or synthesis. Only English-language publications were included.

2.3. Information sources and search strategy

PubMed/MEDLINE, Embase, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar were searched from inception to 5 September 2026. Search terms combined Ang-2-related terms, including “angiopoietin-2,” “angiopoietin 2,” “ANGPT2,” and “Ang-2,” with terms for sepsis and its clinical subtypes and for neonatal and paediatric populations. Controlled vocabulary and database-specific syntax were used where applicable.

One broad and five focused PubMed searches were conducted. For Google Scholar, the first 10 relevance-ranked results for each query were screened. Reference lists of relevant publications were also examined. Additional searches identified the El Gendy study through Google Scholar and the Kortz study through PubMed. The search was restricted to English-language publications. Full database-specific search strategies are provided in Supplementary Table S1, following PRISMA-S guidance (16).

2.4. Study selection

Search results were imported into Rayyan for deduplication and screening. Iqra Paracha and Osama Mohsin independently screened titles and abstracts and assessed potentially eligible full-text reports. Disagreements were resolved by a third reviewer.

Of the 44 records imported into Rayyan, 14 duplicates were removed, leaving 30 records for title and abstract screening. Seventeen records were excluded at this stage, and 13 full-text reports were assessed for eligibility. Two reports were excluded: one lacked an eligible non-septic comparator, and the other did not provide sufficient extractable Ang-2 statistics for the required comparison. Eleven studies were included in the systematic review. The selection process is presented in the PRISMA flow diagram, and the reasons for full-text exclusion are provided in Supplementary Table S7.

2.5. Data extraction

Data were extracted on author, publication year, country, study design, setting, participant characteristics, sepsis definition, comparator group, sample size, specimen type, assay method, sampling time, and reported Ang-2 outcomes. Group-level summary statistics were extracted for participants with sepsis and non-septic controls where available. Findings concerning disease severity, organ dysfunction, mortality, and diagnostic performance were also recorded for narrative synthesis.

Potential participant overlap and repeated episodes were considered when determining suitability for quantitative pooling. Characteristics of the included studies are presented in Supplementary Table S2.

2.6. Outcome and effect measure

The primary outcome was the difference in circulating Ang-2 concentrations between participants with sepsis and non-septic controls. The standardized mean difference (SMD) with a 95% confidence interval (CI) was used to account for differences in measurement scales. A positive SMD indicated higher Ang-2 concentrations in the sepsis group.

When studies reported medians and interquartile ranges or ranges rather than means and standard deviations, estimates were derived using published methods (17, 18). Estimates extracted from published graphs were treated as approximate and included only in the designated sensitivity analysis. Details of the extracted and derived Ang-2 data, including conversions of reported summary statistics and estimates obtained from published graphs, are provided in Supplementary Table S8.

2.7. Risk-of-bias assessment

The methodological quality of the included observational studies was assessed using the Newcastle–Ottawa Scale (NOS), applying the cohort or case-control version as appropriate (19). The scale evaluates selection, comparability, and exposure or outcome ascertainment. Scores were categorized as low risk of bias (7–9 stars), moderate risk (4–6 stars), or high risk (0–3 stars). Summary scores and item-level assessments are provided in Supplementary Tables S3 and S4.

2.8. Statistical analysis

The primary meta-analysis included five studies: El Gendy (2023), Giuliano (2007), Mankhambo (2010), Sallee (2026), and Zonneveld (2017). These studies contributed data from 460 participants with sepsis and 85 non-septic controls, totalling 545 participants. Pooled SMDs and 95% CIs were calculated using an inverse-variance random-effects model in Review Manager (RevMan), version 5.4. Statistical heterogeneity was assessed using the I^2 statistic and the Chi-square test. Heterogeneity was interpreted alongside differences in study populations, sepsis definitions, and study methods (13).

2.9. Sensitivity analyses

Two sensitivity analyses were conducted to assess the robustness of the primary findings.

First, the analysis was repeated after excluding Sallee (2026), leaving four studies with 450 participants with sepsis and 75 controls (525 participants overall). Second, a seven-study analysis added graph-derived estimates from Giuliano (2014) and Siavashi (2017) to the five primary studies. This analysis included 558 participants with sepsis and 146 controls, totalling 704 participants. Because graph-derived estimates were approximate, this analysis was interpreted as a sensitivity analysis rather than the primary result.

2.10. Narrative synthesis

Four studies were not included in the quantitative meta-analysis because their data were unsuitable for a comparable pooled effect estimate. Whitney (2020) reported adjusted associations and diagnostic performance without suitable extractable group-level summary statistics. Kortz (2019) did not provide separate numerical Ang-2 statistics suitable for the eligible comparison. Pierce (2019) reported serial measurements graphically in small groups, with insufficient numerical data for reliable pooling. Çakmakcı (2024) reported repeated febrile-neutropenia episodes without sufficient information to account for participant-level dependence. These studies were retained in the systematic review and synthesized descriptively, in keeping with guidance on alternative synthesis methods (14).

2.11. Reporting bias and certainty of evidence

Publication bias was not formally assessed using funnel plots or statistical tests because fewer than 10 studies contributed to the primary meta-analysis, limiting the reliability of these methods (20).

Certainty in the evidence for the primary outcome was assessed using the GRADE framework (21, 22), considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Observational evidence was initially rated as low certainty and downgraded for serious risk-of-bias concerns and substantial inconsistency. The final certainty rating was very low. The GRADE evidence profile and summary of findings are presented in Supplementary Tables S5 and S6.

2.12. Ethical considerations

This review used data from previously published studies and involved no new data collection from human participants. Additional institutional ethics approval and informed consent were therefore not required.

3. Results

3.1 Study selection

The study selection process is summarized in the PRISMA flow diagram (Fig. 1). A total of 44 records were imported into Rayyan for screening, of which 14 duplicates were removed. The remaining 30 records underwent title and abstract screening, resulting in the exclusion of 17 records. Thirteen full-text articles were assessed for eligibility. Two articles were excluded after full-text assessment: one did not provide an eligible non-septic comparator group, and the other did not report sufficient extractable data

for the comparison of circulating angiopoietin-2 (Ang-2) concentrations between septic and non-septic participants. Eleven studies were included in the systematic review. Of these, five contributed to the primary meta-analysis, while two additional studies were incorporated into a sensitivity analysis using graph-derived estimates. Four studies were synthesized narratively because their findings could not be reliably incorporated into the quantitative analyses.

3.2 Study characteristics

The systematic review included 11 studies investigating circulating Ang-2 in neonatal and pediatric sepsis. The studies included different patient populations and clinical settings, with variation in age, sepsis definitions, comparator groups, specimen types, assay methods, and sampling times. These differences were considered when determining which studies could be combined quantitatively.

Five studies—El Gendy et al. (2023), Giuliano et al. (2007), Mankhambo et al. (2010), Sallee et al. (2026), and Zonneveld et al. (2017)—provided data for the primary meta-analysis. Together, these studies included 460 participants with sepsis and 85 non-septic controls (total N = 545). Two additional studies, Giuliano et al. (2014) and Siavashi et al. (2017), contributed graph-derived estimates for the expanded sensitivity analysis.

Four studies—Whitney et al. (2020), Kortz et al. (2019), Pierce et al. (2019), and Çakmakcı et al. (2024)—were included in the narrative synthesis but not the primary quantitative analysis. Their findings could not be reliably pooled for the prespecified comparison because the required numerical data were unavailable or insufficiently comparable. Study-level characteristics are presented in Supplementary Table S2.

3.3 Risk of bias

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS), with scores of 7–9 classified as low risk of bias, 4–6 as moderate risk, and 0–3 as high risk. Of the 11 included studies, eight were classified as having low risk of bias, while three were classified as having moderate risk of bias: Giuliano et al. (2007), Zonneveld et al. (2017), and Siavashi et al. (2017). No studies were classified as having high risk of bias. The overall NOS assessments are summarized in Supplementary Table S3, and item-level ratings are provided in Supplementary Table S4.

3.4 Primary five-study meta-analysis

The primary meta-analysis included five studies comprising 460 participants with sepsis and 85 non-septic controls (total N = 545). Circulating Ang-2 concentrations were higher in participants with sepsis than in non-septic controls. The pooled standardized mean difference (SMD) was 1.54 (95% confidence interval [CI], 0.91–2.18; $p < 0.00001$), indicating a substantial standardized difference between the groups.

Between-study heterogeneity was considerable (I^2 = 75%), suggesting that the magnitude of the difference varied across studies. The pooled result supports an association between sepsis and higher circulating Ang-2 concentrations, although the degree of heterogeneity limits the interpretation of the estimate as a uniform effect across populations and settings. The study-level estimates and pooled effect are presented in Fig. 2.

3.5 Seven-study sensitivity analysis

A sensitivity analysis expanded the quantitative synthesis to seven studies by incorporating graph-derived estimates from Giuliano et al. (2014) and Siavashi et al. (2017). This analysis included 558 participants with sepsis and 146 non-septic controls (total N = 704).

The pooled SMD was 3.86 (95% CI, 2.01–5.70; $p < 0.0001$). Heterogeneity was very high (I^2 = 97%), indicating substantial variation in the estimated effects across studies. Although the pooled difference remained positive, its magnitude was considerably greater than that observed in the primary analysis. The increased heterogeneity and reliance on graph-derived estimates warrant caution when interpreting this expanded analysis. The results are presented in Fig. 3.

3.6 Sensitivity analysis excluding Sallee et al.

A sensitivity analysis was performed after excluding Sallee et al. (2026), leaving four studies with 450 participants with sepsis and 75 non-septic controls (total N = 525). The pooled SMD was 1.41 (95% CI, 0.74–2.09; $p < 0.0001$), with substantial between-study heterogeneity (I^2 = 78%).

The direction and statistical significance of the pooled association were maintained after exclusion of this study. The estimate was similar to that of the primary analysis, suggesting that the finding of higher circulating Ang-2 concentrations in sepsis was not dependent solely on the inclusion of Sallee et al. Heterogeneity remained considerable. The results are presented in Fig. 4.

3.7 Narrative synthesis of four non-pooled studies

Four studies including Whitney et al. (2020), Kortz et al. (2019), Pierce et al. (2019), and Çakmakcı et al. (2024) were included in the systematic review but were not incorporated into the primary meta-analysis. Their findings could not be reliably pooled for the prespecified comparison of circulating Ang-2 concentrations between septic and non-septic participants because the required numerical data were unavailable or insufficiently comparable.

These studies were retained in the narrative synthesis to ensure that relevant evidence was represented in the systematic review. Their findings were considered separately from the pooled estimates, and no additional quantitative effect estimate was calculated for this group. The study-specific findings and reasons for non-pooling are summarized in Supplementary Table S2.

3.8 Certainty of the evidence

The certainty of evidence for the primary five-study meta-analysis was assessed using the GRADE framework. Because the evidence was derived from observational studies, certainty initially started at a low level. The evidence was downgraded for serious concerns regarding risk of bias and inconsistency, particularly the substantial between-study heterogeneity observed in the primary analysis.

The overall certainty of evidence was rated as **very low**. Accordingly, although the pooled findings indicated higher circulating Ang-2 concentrations in neonates and children with sepsis than in non-septic controls, confidence in the magnitude and generalizability of this difference remains limited. The GRADE evidence profile and summary of findings are provided in Supplementary Tables S5 and S6.

3. Results

3.1 Study selection

Of 44 records identified for screening, 14 duplicates were removed, leaving 30 records for title and abstract screening. Seventeen records were excluded, and 13 full-text articles were assessed for eligibility. Two full-text articles were excluded, leaving 11 studies for the systematic review (Fig. 1). Five studies contributed to the primary meta-analysis, two additional studies were incorporated into the seven-study sensitivity analysis, and four studies were included in the narrative synthesis.

3.2 Study characteristics

The primary meta-analysis comprised five studies: El Gendy et al. (2023), Giuliano et al. (2007), Mankhambo et al. (2010), Sallee et al. (2026), and Zonneveld et al. (2017). These studies contributed 460 participants with sepsis and 85 non-septic controls. Giuliano et al. (2014) and Siavashi et al. (2017) were added to the expanded sensitivity analysis using graph-derived estimates. The four studies not included in the primary quantitative analysis were Whitney et al. (2020), Kortz et al. (2019), Pierce et al. (2019), and Çakmakcı et al. (2024). Detailed study-level data are provided in Supplementary Table S2.

3.3 Risk of bias

Of the 11 included studies, eight (72.7%) received Newcastle–Ottawa Scale scores of 7–9 and were classified as having low risk of bias. Three (27.3%) received scores of 4–6 and were classified as having moderate risk of bias: Giuliano et al. (2007), Zonneveld et al. (2017), and Siavashi et al. (2017). No study was classified as having high risk of bias. The revised NOS score for Giuliano et al. (2007) was 6/9. Study-level scores and item-level assessments are reported in Supplementary Tables S3 and S4, respectively.

3.4 Primary five-study meta-analysis

The primary meta-analysis included 545 participants (460 with sepsis and 85 controls). The pooled standardized mean difference (SMD) in circulating angiopoietin-2 (Ang-2) concentrations was 1.54 (95% CI, 0.91–2.18; $p < 0.00001$), indicating higher Ang-2 concentrations in the sepsis group. Between-study

heterogeneity was substantial (I^2 = 75%). The forest plot and individual study estimates are presented in Fig. 2.

3.5 Seven-study sensitivity analysis

The expanded analysis included all five primary studies plus Giuliano et al. (2014) and Siavashi et al. (2017), for a total of seven studies and 704 participants (558 with sepsis and 146 controls). Both additional studies contributed graph-derived estimates. The pooled SMD increased to 3.86 (95% CI, 2.01–5.70; $p < 0.0001$), while heterogeneity increased to I^2 = 97%. Compared with the primary analysis, the pooled estimate was larger by 2.32 SMD units, with a 22-percentage-point increase in I^2. The expanded estimate therefore showed greater between-study variability and was sensitive to inclusion of the two additional studies (Fig. 3).

3.6 Sensitivity analysis excluding Sallee et al.

Excluding Sallee et al. (2026) from the primary analysis left four studies, comprising 525 participants (450 with sepsis and 75 controls). The pooled SMD was 1.41 (95% CI, 0.74–2.09; $p < 0.0001$), with I^2 = 78%. Relative to the primary analysis, the pooled SMD decreased by 0.13, while heterogeneity increased by three percentage points. The association remained statistically significant and in the same direction after exclusion of Sallee et al. (Fig. 4).

3.7 Narrative synthesis of four non-pooled studies

Four studies including Whitney et al. (2020), Kortz et al. (2019), Pierce et al. (2019), and Çakmakcı et al. (2024) were retained in the systematic review but did not contribute to the primary pooled estimate. Their data could not be reliably incorporated into the prespecified quantitative comparison. Accordingly, no pooled effect estimate was calculated for these four studies. Their individual findings and reasons for non-pooling are documented in Supplementary Table S2.

3.8 Certainty of the evidence

The GRADE assessment rated the certainty of evidence for the primary five-study meta-analysis as very low. The evidence was downgraded for concerns regarding risk of bias and inconsistency, consistent with the substantial heterogeneity observed in the primary analysis (I^2 = 75%). The pooled estimate indicated higher circulating Ang-2 concentrations in participants with sepsis; however, the very-low-certainty rating limits confidence in the magnitude and generalizability of this estimate. The GRADE evidence profile and summary of findings are presented in Supplementary Tables S5 and S6.

4. Discussion

4.1. Principal findings

This systematic review and meta-analysis found higher circulating Ang-2 concentrations in neonates and children with sepsis than in non-septic controls. In the primary five-study analysis, the pooled SMD was

1.54 (95% CI, 0.91–2.18), with substantial heterogeneity (I^2 = 75%). Excluding Sallee et al. produced a similar estimate, whereas adding two studies using graph-derived estimates increased the pooled effect and heterogeneity markedly. These findings support an association but indicate that its magnitude is uncertain and not uniform across settings.

The sensitivity analyses should be interpreted as tests of analytical robustness, not independent replications, because they reuse studies from the primary analysis. The similarity of the four-study estimate suggests that the primary direction was not dependent solely on Sallee et al. Conversely, the expanded analysis shows that the magnitude was sensitive to the additional studies and approximate graph extraction. The overall GRADE certainty was very low, limiting confidence in generalizability.

4.2. Biological and clinical context

The association is biologically plausible. Ang-1 generally supports endothelial stability through Tie2 activation, whereas Ang-2 can oppose this signalling under inflammatory conditions (5, 6). Endothelial destabilization may contribute to vascular permeability, capillary leakage, and microcirculatory dysfunction. Experimental research has also implicated Ang-2 in sepsis-associated organ dysfunction and mortality (24).

Pediatric studies provide related but not interchangeable evidence. Giuliano et al. reported higher plasma Ang-2 in children with septic shock than in healthy and critically ill comparator groups and described temporal changes in angiopoietins across sepsis severity (8, 9). Zonneveld et al. found higher serum Ang-2 and Ang-2/Ang-1 ratios in newborns with culture-positive early-onset sepsis (11). Wang et al. investigated Ang-1, Ang-2, and bicarbonate as a potential biomarker panel for severity classification (10). These studies support investigation of Ang-2 but differ in population, clinical question, comparator, and timing.

Prognostic associations should be distinguished from diagnostic group differences. In children with severe bacterial infection, Mankhambo et al. observed higher Ang-2 among non-survivors in unadjusted comparisons, but Ang-2 was not independently associated with mortality after adjustment (12). Likewise, adult evidence on Ang-2 and mortality cannot validate pediatric diagnostic utility: Zhuo et al. synthesized 33 adult studies involving 4,703 participants and assessed prognosis, whereas this review compared septic with non-septic pediatric participants (23). Age, comparator, and outcome differences limit direct extrapolation.

4.3. Heterogeneity and sensitivity analyses

Substantial heterogeneity may reflect differences in age, sepsis definitions and severity, comparator selection, specimen type, assay methods, and sampling time. A healthy control group provides a different contrast from hospitalized children with alternative inflammatory conditions; a biomarker that separates sepsis from health may not reliably distinguish sepsis from other illnesses encountered clinically. Previous reviews have highlighted the difficulty of translating endothelial-biomarker associations into validated tests (7).

The available number of studies did not permit reliable investigation of these potential sources through subgroup analyses or meta-regression. Serial measurements and temporal changes reported in pediatric studies further suggest that sampling time may influence concentrations (9). Future studies should report age, clinical severity, comparator characteristics, specimen, assay platform, and sampling time consistently.

The expanded sensitivity analysis increased the pooled SMD to 3.86 and I^2 to 97% after adding Giuliano et al. (2014) and Siavashi et al. (2017) using graph-derived estimates. Graph extraction is approximate and introduces additional uncertainty; the larger estimate may reflect study differences, extraction imprecision, or both. It should not be interpreted as stronger evidence. In contrast, excluding Sallee et al. resulted in a similar estimate (SMD, 1.41) but did not remove heterogeneity or independently validate the result.

4.4. Strengths and limitations

This review focused on a clearly defined comparison and distinguished a five-study primary analysis from sensitivity analyses using alternative inclusion decisions. Approximate graph-derived estimates were kept out of the primary analysis, and relevant studies that could not be pooled were retained for narrative synthesis. Risk of bias and certainty of evidence were assessed rather than interpreting statistical significance alone.

Several limitations should be considered. The primary meta-analysis included only five studies, restricting the ability to explore heterogeneity or compare neonatal and older pediatric populations. Considerable heterogeneity means the pooled estimate may not represent a common effect across clinical settings. The observational evidence establishes neither causality nor independent diagnostic or prognostic value. The expanded analysis relied partly on approximate graph-derived values, while four studies could not contribute to the pooled estimate because their data were unavailable or unsuitable for direct comparison. Finally, very-low-certainty evidence limits confidence in the magnitude and generalizability of the association.

4.5. Implications for research and practice

The current findings do not justify using Ang-2 as a standalone diagnostic or prognostic test. Further prospective, multicentre studies should use clear sepsis criteria, clinically relevant comparator groups, standardized assays, and prespecified sampling times. Diagnostic studies should evaluate discrimination from alternative conditions and report test-performance measures; prognostic studies should assess prespecified outcomes and determine whether Ang-2 adds information beyond established clinical variables.

Assay standardization, validated performance, and clinically established thresholds remain important barriers to clinical implementation of endothelial-activation biomarkers (7). External validation and clinical-utility studies are needed to determine whether adding Ang-2 to assessment pathways changes

decisions or improves outcomes. Until then, Ang-2 should be regarded as a candidate marker associated with pediatric sepsis, not a validated standalone clinical test.

5. Conclusion

Circulating Ang-2 concentrations were higher in neonates and children with sepsis than in non-septic controls. However, substantial heterogeneity, sensitivity of the pooled magnitude to study inclusion, and very-low-certainty evidence limit confidence in the consistency and generalizability of this association. Prospective research using standardized measurements, clinically relevant comparators, and independent validation is needed to determine whether Ang-2 provides meaningful diagnostic or prognostic information.

Abbreviations

Ang-1
angiopoietin-1
Ang-2
angiopoietin-2
CENTRAL
Cochrane Central Register of Controlled Trials
CI
confidence interval
GRADE
Grading of Recommendations Assessment,Development and Evaluation
NOS
Newcastle–Ottawa Scale
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SMD
standardized mean difference.

Declarations

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Author contributions

Saweera Khan contributed to conceptualization, data curation, writing – original draft, and validation. Iqra Paracha contributed to investigation, formal analysis, writing – original draft, and validation. Osama Mohsin contributed to investigation, methodology, writing – review and editing, and validation. Iqra Tanzeel contributed to formal analysis, writing – review and editing, and validation. All authors reviewed and approved the final manuscript and agree to be accountable for their contributions to the work.

Declaration of interest

The authors declare no competing interests.

Funding statement

This research received no external funding.

Data availability statement

The data supporting this systematic review and meta-analysis were obtained from previously published studies. Extracted study characteristics and supporting information are provided in the article and supplementary materials. No new primary participant-level data were collected.

Ethics statement

Ethics approval was not required because this systematic review and meta-analysis used data from previously published studies and involved no new data collection from human participants.

Consent for publication

Not applicable. This article does not contain identifiable personal information or images requiring consent for publication.

Registration

The review protocol was registered in PROSPERO under registration number CRD420261519673 on 27 September 2026 and last updated on 28 September 2026.

Declaration of generative-AI use

OpenAI ChatGPT (GPT-6) was used during manuscript preparation to assist with revising text, organizing sections, and refining language. The authors are responsible for critically reviewing the generated material, verifying scientific claims and references against the original sources, and ensuring the accuracy, originality, and integrity of the final manuscript.

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Figures

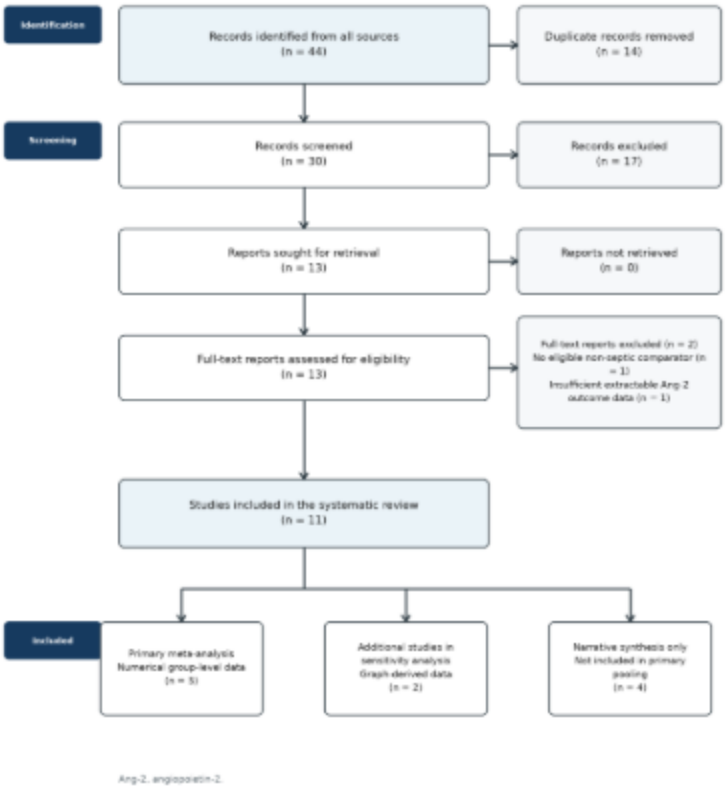


Figure 1

PRISMA 2020 flow diagram showing the identification, screening, full-text assessment, and inclusion of studies in the systematic review and meta-analysis.

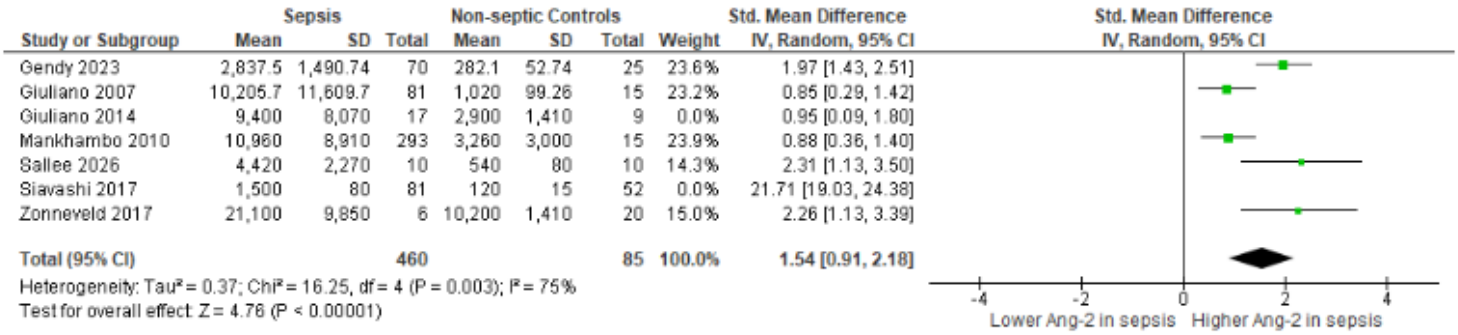


Figure 2

Forest plot of the primary five-study meta-analysis comparing circulating angiopoietin-2 (Ang-2) concentrations in neonates and children with sepsis versus non-septic controls. The pooled standardized mean difference (SMD) was calculated using an inverse-variance random-effects model. Positive SMD values indicate higher Ang-2 concentrations in the sepsis group.

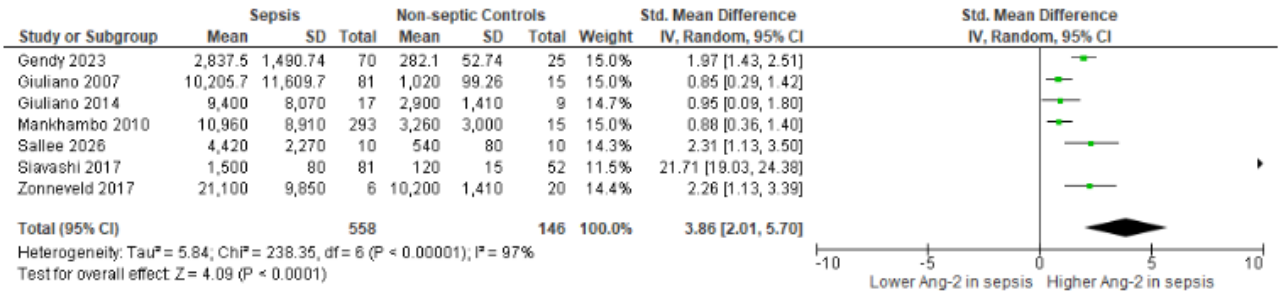


Figure 3

Forest plot of the seven-study sensitivity analysis comparing circulating Ang-2 concentrations between participants with sepsis and non-septic controls. This analysis included the five studies from the primary meta-analysis and two additional studies with estimates derived from published graphs.

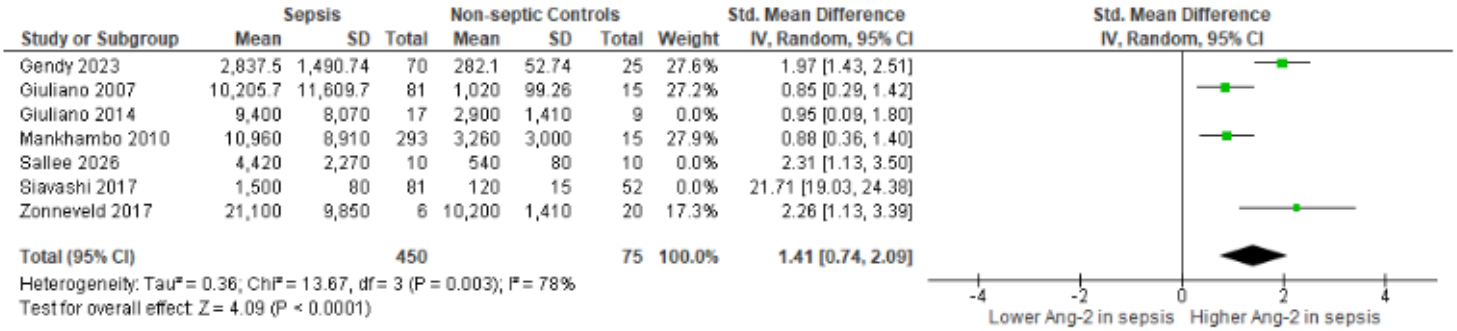


Figure 4

Forest plot of the sensitivity analysis excluding Sallee et al. (2026) from the primary meta-analysis. The analysis included the four remaining studies and compared circulating Ang-2 concentrations between participants with sepsis and non-septic controls.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterials.docx